The Pending Claims

Claims 1-10 and 12-27 are currently pending. The Examiner renumbered claims 34-41, submitted with the preliminary amendment, as claims 18-25, and the dependencies have been adjusted as such. Claims 26 and 27 have been added, and claim 11 has been canceled.

The Office Action

The Office states that the oath or declaration is allegedly not in compliance with 37 CFR 1.52(c). The Office states that the sequence listing allegedly is not in compliance with 37 CFR § 1.821(a) and (d). Claim 11 has been rejected to under 37 CFR § 1.75 as allegedly being a substantial duplicate of claim 10. Claims 1-8 and 17 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 2, 5, 6, 8, and 13 of U.S. Patent No. 6,126,965. Claims 9-15 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-6 of U.S. Patent No. 6,333,314. Claim 16 has been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 7 of U.S. Patent No. 6,333,314. Claims 18-20 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 1 of U.S. Patent No. 6,333,314. Claims 18-25 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled. Claim 1 has been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Epand et al. (U.S. Patent No. 5,283,185). Claims 18-25 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Patel et al. (*Molecular Carcinogenesis*, 1993 Vol. 8:7-12), Kasid et al. (*Science*, 1989 Vol. 243:1354-1356), Monia et al. (U.S. Patent No. 5,952,229) in further view of Epand et al. and Seung et al. (*Cancer Research*, 1995 Vol. 55:5561-5565).

The Amendments to the Specification and Claims

The specification has been amended to identify the sequence disclosed on page 3, line 9 as SEQ ID NO: 1. Furthermore, all "Seq. #" identifiers were changed to recite "SEQ ID NO:".

A Sequence Listing for the sequence disclosure on page 4, line 29 is enclosed herewith.

Claims 26 and 27 have been added to recite administration of the oligonucleotide in accordance with the method of claim 18. Support for claims 26 and 27 can be found in the specification at, for example, page 10, line 23 and page 12, line1.

Claim 11 has been canceled.

Claims 4, 9, 15 and 16 have been amended to recite a "SEQ ID NO: 1" following the nucleotide sequence in the claim.

Claim 4 has been amended to remove an extra "C" in the nucleotide sequence to properly characterize it as SEQ ID NO: 1. Support for this sequence is found in the specification at, for example, page 2, line 5.

Claim 15 has been amended to remove the word "only" due to its redundancy.

No new matter has been added by way of these amendments. Separate documents setting forth the precise changes to the specification and claims, as well as the text of all pending claims, are enclosed herewith.

Discussion of the Rejection under 35 U.S.C. § 112, first paragraph

Claims 18-25 have been rejected under 35 U.S.C. Section 112, first paragraph, for allegedly lacking enablement. The Office contends that the specification is enabling for a method of administering antisense raf of the nucleotide sequence 5' –GTGCTCCATTGATGC- 3' intratumorally in immunocompromised mice, but allegedly does not reasonably provide enablement for the radiosensitization of all tumors in all organisms wherein an oligonucleotide is administered *in vivo* to all organisms. This rejection is traversed for the reasons set forth below.

Applicants direct the Office's attention to the specification at, for example, page 18, lines 8-17, where liposome encapsulated oligodeoxyribonucleotides were detected up to 48 hours post administration, and were detected in all organs. Such ubiquitous localization and sustainability of liposome oligonucleotides sufficiently enables those skilled in the art to radiosensitize radio resistant tumors in accord with the method of claims 18-25. Furthermore, newly added claims 26 and 27 are directed to the administration of oligonucleotides in accordance with the disclosed method of claim 18 and are supported by the specification at, for example, page 10, line 23 and page 12, line 1.

The Office characterizes the subject claims as directed to gene therapy. However, no claim of the present application requires vector-enhanced targeting of nucleic acid sequences or recites the phrase "gene therapy."

Therefore, in view of the foregoing, Applicants submit that the specification is enabling for one of ordinary skill in the art to make and use the present invention and thus, Applicants hereby request that rejections of claims 18-25 for alleged lack of enablement be withdrawn.

Discussion of the Rejection under 35 U.S.C. § 102

Claim 1 has been rejected under Section 102(b) as allegedly anticipated by Epand et al. (U.S. Patent No. 5,283,185).

The rejected claim is drawn to a composition comprising a cationic liposome containing a cationic lipid, phosphatidylcholine and cholesterol. Epand et al. notes that the cationic lipid used in the method disclosed therein "has a structure which includes a lipophilic group *derived from* cholesterol (column 3, lines 12-13). However, Epand et al. does not disclose a liposome containing cholesterol and, therefore, does not anticipate claim 1. Therefore, the rejection under Section 102(b) should be withdrawn.

Discussion of the Rejection under 35 U.S.C. § 103(a)

The Office has rejected claims 18-25 under Section 103(a) as allegedly being obvious, therefore, unpatentable over Patel et al. (*Molecular Carcinogenesis*, 1993 Vol. 8: 7-12), Kasid et al. (Science, 1989 Vol. 243: 1354-1356), Monia et al. (U.S. Patent No. 5,952,229) and further in view of Epand et al. (U.S. Pat. No. 5,283,185). In particular, the Office cites Patel et al. as teaching the direct administration of antisense oligonucleotides to cancer cells in order to increase radiosensitivity of target cells; Kasid et al. as teaching the effect of antisense c-raf-1 on tumorigenicity and radiation sensitivity of human laryngeal squamous carcinoma; Monia et al. as teaching the design and use of antisense oligonucleotides of no more than 40 bases, comprising the sequence 5' –GTGCTCCATTGATGC- 3', whereby the oligo is administered locally to the site of the tumor; Epand et al. as noted above; and Seung et al. as teaching combined gene therapy using cationic liposomes prior to radiation, together or separate with radiation to overcome tumor resistance to cytotoxic agents in murine tumor cells. The rejection is traversed for the reasons set forth below.

In order to establish a prima facie case of obviousness, the Office must satisfy three requirements: (1) the Office must identify some suggestion or motivation, either in the references relied upon or in the knowledge generally available in the art, to modify the references in such a way as to arrive at the invention claimed, (2) there must be a reasonable expectation of success, and (3) the prior art references relied upon must teach or suggest all of the elements of the claim. The Office Action has not met this burden.

The Office cites Epand et al. as teaching the synthesis and use of cationic liposomes comprising a cationic lipid, phosphatidylcholine and cholesterol in an isotonic, pharmaceutically acceptable carrier. However, this is not an accurate characterization of Epand et al. As noted above, Epand et al. does not disclose a liposome containing cholesterol. Furthermore, no other cited prior art reference satisfies the deficiencies of Epand et al. Thus, given this deficiency in the cited art, one of ordinary skill in the art would

not be let to the present invention even if (s)he were motivated to make the proffered combination. For this reason alone, the rejection should be withdrawn.

Rather than providing a motivation to produce the claimed invention, the cited art actually teaches away from the subject matter recited by the pending claims. For example, Seung et al. discloses the use of liposomes carrying the nucleic acid encoding tumor necrosis factor-α (TNF-α), however Seung et al. notes that it is the resultant TNF-α *protein* that increases tumor sensitivity and not the nucleotide sequence itself, whereas the invention of claim 18 requires specific activity of the oligonucleotide. Thus Seung et al. actually teaches away from the present invention, which further evinces its unobviousness.

Therefore, the prior art references do not suggest all the elements of the rejected claims. Nor has the Office Action provided objective evidence that one of ordinary skill in the art, faced with the disclosures of the cited references, would be motivated to combine them at all, much less in the particular manner required to arrive at the invention as claimed in the rejected claims (as opposed to some other manner). Accordingly, the rejection of these claims under Section 103(a) should be withdrawn. Additionally, the cited references, taken together or separately, do not disclose or suggest all of the elements of the claims.

Discussion of the Nonstatutory Double Patenting Rejection

Claims 1-8 and 17

Claims 1-8 and 17 stand rejected under the judicially created doctrine of nonstatutory double patenting over claims 1, 2, 5, 6, 8 and 13 of U.S. Patent No. 6,126,965 (the '965 patent). Specifically, the Office alleges that, although the conflicting claims are not identical, they are not patentably distinct from the claims of the '965 patent. This rejection is traversed for the reasons set forth below. Since the pending application is a continuation of an abandoned divisional application of the '965 patent, a double patenting rejection of these claims is improper (M.P.E.P at § 804, Subsection II). Therefore, Applicants hereby request that the nonstatutory double patenting rejection of claims 1-8 and 17 be withdrawn.

Claims 9-16 and 18-20

Claims 9-16 and 18-20 stand rejected under the judicially created doctrine of nonstatutory double patenting over claims 1-7 of U.S. Patent No. 6,333,314 (the '314 patent). Claim 11 is canceled due to its duplicative nature of claim 10. The Office alleges that, although the conflicting claims are not identical, they are not patentably distinct for methods of radiosensitizing a tumor or a composition of matter comprising liposomes containing the sequence of SEQ ID NO: 1. This rejection is traversed for the reasons set forth below.

Claims 9-15 of the instant application are patentably distinct from claims 1-6 of the '314 patent. Claim 1 of the '314 patent incorporates the limitation of a composition of a cationic liposome, phosphatidylcholine and cholesterol where as claims 9-15 of the instant application do not require such elements to carry out their method of use. Furthermore, claim 16 of the instant invention recites a pharmaceutically acceptable carrier and a generic composition of liposome. In contrast, claim 7 of the '314 patent does not recite the use of a pharmaceutically acceptable carrier, nor has the Office offered any objective evidence that the generic composition of liposome of pending claim 16 would be obvious in view of the specific liposomal species recited in claim 7 of the '314 patent.

Finally, claims 18-20 of the instant application are patentably distinct from claim 1 of the '314 patent. Claim 19 of the instant application recites oncogenes (ras, raf, cot, mos and myc) which are not recited by the claims of the '314 patent.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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